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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,311	01/24/2002	Claas Junghans	NHL-NP-37	1924

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,311	JUNGHANS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 43-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 53-59* is/are rejected.

7)☒ Claim(s) *43-52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-17-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-5-03.

Claims 1-3, 43-59 are pending in the instant application.

Election/Restriction

Applicant's election with traverse of SEQ ID NO: 1 in Paper No. 12-5-03 is acknowledged. The traversal is on the ground(s) that 4 sequences is well under the maximum number of 10 sequences suggested by the MPEP and that since the sequences claimed are not complex, then no undue burden exists to examine all of the sequence originally claimed. This is not found persuasive because searching of all of the sequences claimed would require a separate search of an expansive and burgeoning art and corresponding data bases for each sequence claimed, and would represent a serious burden to both the examiner and the facilities of the PTO.

Applicant asserts that the MPEP states that a reasonable number of sequences are to be searched, according to the restriction guidelines, and this has historically included up to 10 nucleotide sequences. The guidelines that Applicant refers to were established before the art and corresponding data bases were as expansive as they now exist. A more recent guideline limits searches to a single sequence, not ten sequences.

The requirement is still deemed proper and is therefore made FINAL.

SEQ ID Nos: 2 and 3 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12-5-03. The claims have been examined on their merits as they pertain to the elected SEQ ID NO: 1, as set forth in the Office action below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 53, lines 1-2, it is unclear what is meant or encompassed by "humans or higher animals" (e.g. Does this refer to animals higher than humans, or against some phylogenetic threshold?) Appropriate clarification is requested.

Claims 1-3, 53-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods of immunostimulation of humans or higher animals using partially single stranded, dumbbell shaped, covalently closed deoxyribonucleic acid molecules containing one or more sequences having the formula: $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine, whereby effector cells of an immune system are activated, an immune response against antigens which are not activated during MHC-1 presentation is induced, and tolerance against autoantigens is broken. The claims are also drawn to methods of immunostimulation of humans or higher animals using dumbbell-shaped, covalently closed deoxyribonucleic acid molecules containing one or more neutralizing CpG motifs for blocking stimulation effects of ISS. The specification and claims do not indicate what distinguishing attributes are concisely shared by members of the broad genus comprising nucleic acids $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine, or further comprising neutralizing CpG motifs for blocking stimulation effects of ISS. Nor are the distinguishing attributes or characteristics concisely described for members of the broad genera comprising activated effector cells of an immune system, nor comprising antigens not activated during MHC-1 presentation.

The scope of the claims includes numerous structural variants, and the genera are highly variant because a significant number of structural differences between

members of the various genera are permitted. Concise structural features that could distinguish structures within each genus from others are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in the genus comprising $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine, or further comprising neutralizing CpG motifs for blocking stimulation effects of ISS, nor activated effector cells of an immune system, nor antigens which are not activated during MHC-1 presentation, nor the genus comprising humans or higher animals, such that the characteristics concisely identifying members of the proposed genera are adequately exemplified. And because the genera are highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe these various genera claimed. Thus, Applicants were not in possession of the very broadly claimed genera.

Claims 53-55 and 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro reduction of IgE production in human PBMCs following administration of SEQ ID NO: 4, the in vivo increase in anti-HbsAg IgGs following IP administration of SEQ ID NO: 4 in mice, and increased IFN-gamma production in CD14 positive dendritic mouse cells in vitro following administration of prostaglandin E12, TNF-alpha and SEQ ID NO: 4, does not

reasonably provide enablement for activation of any effector cells of any immune system in humans or higher animals, for induction of an immune response against any antigen not activated during MHC-1 presentation in humans or higher animals, for breaking tolerance against autoantigens in humans or higher animals, repolarizing a type-2 immune response to type-1 in humans or higher animals, or of blocking stimulation effects of ISS comprising the administration of nucleic acids further comprising neutralizing CpG motifs in humans or higher animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of immunostimulation of humans or higher animals using partially single stranded, dumbbell shaped, covalently closed deoxyribonucleic acid molecules containing one or more sequences having the formula: $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine, whereby effector cells of an immune system are activated, an immune response against antigens which are not activated during MHC-1 presentation is induced, and tolerance against autoantigens is broken. The claims are also drawn to methods of immunostimulation of humans or higher animals using dumbbell-shaped, covalently closed deoxyribonucleic acid molecules containing one or more neutralizing CpG motifs for blocking stimulation effects of ISS.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms (See Krieg et al Immunology Today 21(1): 521-526, 2000), Weiner (J. of Leukocyte Biol. 68: 455-463, 2000) and McCluskie et al (Molecular Med. 5(5): 287-300, 1999) for recent advances using CpG oligonucleotides). Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and depending upon the organism (See McCluskie et al in its entirety, and especially on page 296; Also see Krieg et al on page 524). Weiner states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (See especially page 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (See Agrawal et al especially on pages 78-80; See also pages 31-32 of the instant specification).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of activating all types of effector cells of any immune system in humans or other higher animals, a method of inducing immune

responses against any antigen not activated during MHC-1 presentation, a method for breaking tolerance against any autoantigens, or for blocking immune stimulation of immunostimulatory sequences (ISS) using these covalently closed deoxyribonucleic acid molecules further comprising one or more neutralizing CpG motifs. The specification teaches an increase in anti-HbsAg IgGs in mice following IP administration of SEQ ID NO: 4, and an increase IFN-gamma production in CD14 positive dendritic mouse cells in vitro following administration of prostaglandin E12, TNF-alpha and SEQ ID NO: 4. The specification also teaches a reduction of IgE production in vitro in isolated human PBMCs, following administration of SEQ ID NO: 4.

One skilled in the art would not accept on its face these examples given in the specification as being correlative or representative of the successful activation of all effectors cells of any immune system in humans or any other higher animal, the successful immune response induction against any antigen not activated during MHC-activation, the successful breaking of tolerance against any autoantigen in humans or any higher animal, or the successful block in immune stimulation of any ISS using the deoxyribonucleic acid molecules claimed, and further comprising any neutralizing CpG motifs, in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided in vivo in humans or other higher organisms upon administration via any route of the instantly claimed dumbbell-shaped, CpG.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods of immunostimulation of humans or higher animals using partially single stranded, dumbbell shaped, covalently closed deoxyribonucleic acid molecules containing one or more sequences having the formula: $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine, whereby effector cells of an immune system are activated, an immune response against antigens which are not activated during MHC-1 presentation is induced, and tolerance against autoantigens is broken. The claims are also drawn to methods of immunostimulation of humans or higher animals using dumbbell-shaped, covalently closed deoxyribonucleic acid molecules containing one or more neutralizing CpG motifs for blocking stimulation effects of ISS.

Since the specification fails to provide particular guidance for a method of activating all types of effector cells of any immune system in humans or other higher animals, a method of inducing immune responses against any antigen not activated during MHC-1 presentation, a method for breaking tolerance against any autoantigens, or for blocking immune stimulation of immunostimulatory sequences (ISS) using these covalently closed deoxyribonucleic acid molecules further comprising one or more neutralizing CpG motifs in humans or any higher animal, and since determination of these factors for a particular CpG containing oligonucleotide and for a particular route of

administration and organism is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al in view of the combined teachings of Erie et al and Wolters et al.

The claims are drawn to compositions comprising partially single stranded, dumbbell shaped, covalently closed deoxyribonucleic acid molecules containing one or more sequences having the formula: $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group

consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine.

Krieg et al (Nature 374: 546-9, 1995, IDS document **AG,** submitted 6-17-02) teach deoxyribonucleic acid molecules containing one or more sequences having the formula: $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine (see table 1, page 548).

Krieg et al do not teach dumbbell shaped, covalently closed deoxyribonucleic acid molecules between 40 and 200 nucleotides.

Erie et al (Biochemistry 26 : 7150-7159, 1987) teach dumbbell shaped, covalently closed deoxyribonucleic acid molecules (see the abstract, fig. 1 on page 7151, tables 1 on page 7153, fig. 7 on page 7155 and figure 8 on page 7156).

Wolters et al (Nucleic Acids Res. 17 (13): 5163-5172, 1989) teach dumbbell shaped, covalently closed deoxyribonucleic acid molecules between 40 and 200 nucleotides, which molecules are resistant to exonuclease degradation (see especially the abstract, figure 3 on page 5168, second paragraph on page 5169-top line on page 5170).

It would have been obvious to one of ordinary skill in the art to generate a dumbbell shaped, covalently closed deoxyribonucleic acid molecules comprising one or more sequences having the formula: $N^1N^2CGN^3N^4$, wherein N^1N^2 is selected from the group consisting of GT, GG, GA, AT and AA and N^3N^4 is selected from the group

consisting of CT, TT, C deoxycytosine, G deoxyguanosine, A deoxyadenosine and T deoxythymidine because Krieg et al previously taught various CpG containing ISS adhering to this formula and Erie and Wolters et al taught the generation of dumbbell shaped, covalently closed deoxyribonucleic acid molecules between 40 and 200 nucleotides. One of ordinary skill in the art would have been motivated to generate the dumbbell shaped deoxyribonucleic acid molecules because Krieg et al teach the immunostimulatory properties of CpG containing ISS, and Erie and Wolters teach the technique to covalently close these small nucleic acid molecules. Furthermore, Wolters et al teach the enhanced stability of covalently closed nucleic acid molecules over linear nucleic acid molecules. One of ordinary skill in the art therefore would have expected that such CpG containing molecules would have enhanced stability from exonucleoase digestion and would provide immunostimulation of some effector cells of an immune system in vitro.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

The sequences of SEQ ID Nos: 1 and 5 appear free of the prior art of record. Claims 43- 52 are objected to because they are found allowable with regard to the elected sequence(s) SEQ ID Nos: 1 and 5, but the claims also contain non-elected sequences SEQ ID Nos: 2 and 3.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ
2-19-04